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REVIEW ARTICLE
Discernment between deliberate and natural infectious disease outbreaks

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SUMMARY

Public health authorities should be vigilant to the potential for outbreaks deliberately caused by biological agents (bioterrorism). Such events require a rapid response and incorporation of non-traditional partners for disease investigation and outbreak control. The astute application of infectious disease epidemiological principles can promote an enhanced index of suspicion for such events. We discuss epidemiological indicators that should be considered during outbreak investigations, and also examine their application during bioterrorism incidents, an accidental release of an agent, outbreaks of infections that were alleged to have been deliberately initiated, and a model scenario. The Grunow & Finke epidemiological assessment tool is used to examine these historical events and the model scenario. The results received from this analysis, coupled with an understanding of epidemiological clues to unnatural events, and knowledge of how to manage such events, can aid in the improved response and resolution of epidemics.

INTRODUCTION

Successful management of infectious disease transmission in a population, whether naturally occurring or deliberately caused (bioterrorism), is directly related to event recognition. In Yugoslavia in 1972, one unrecognized smallpox case led to 11 unrecognized secondary cases. Within weeks, a massive vaccination effort and border closure occurred in response to 175 smallpox cases and 35 subsequent deaths [1]. Early recognition of secondary cases may have significantly modified the eventual outcome. One simulation study of a smallpox outbreak showed that the more rapid the intervention, including quarantine and vaccination, the greater the chances of halting disease spread [2]. It is unlikely that a bioterrorism event would be considered initially by medical professionals, especially if the disease presentation is similar to other diseases that might be expected to occur, such as seasonal influenza. Physicians are taught first to consider common illnesses and may diagnose an endemic disease before a new or emerging disease, a laboratory accident or a deliberately caused epidemic [3]. Therefore, care providers should have some familiarity with those diseases expected when caused by bioterrorism agents [4], and a healthy 'index of suspicion' if they are to recognize an event early enough to make significant modifications to the outcome [5].

This review presents three categories of epidemiological case studies that illustrate: deliberately

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caused epidemics, an accidental release of a biological warfare (BW) agent, and natural outbreaks that may mimic bioterrorism. Potential epidemiological clues are provided to discern more ably a deliberately caused outbreak. These clues are linked to the epidemiological case studies to illustrate their application. An epidemiological assessment tool is applied to these case studies that may help public health authorities to determine if a biological agent has been deliberately used to initiate an epidemic. Management methods used for the control of infectious disease outbreaks are presented, as is a likely scenario of how the clues, management methods, and epidemiological assessment tool could be used for deliberately caused outbreaks of concern.

Epidemiological case studies

The following epidemiological case studies are presented to illustrate the differences between deliberate and naturally occurring epidemics. Historical biological attacks and some naturally occurring epidemics are considered in this context.

Deliberate epidemics (bioterrorism)

The first three case studies were deliberately caused bioterrorism events that occurred in the United States. These events were not recognized immediately as intentional. In the anthrax mailings of 2001, the agent was recognized as intentionally spread within days to weeks. This is a dramatic improvement over a 1984 salmonellosis outbreak in Oregon, which was not recognized as bioterrorism for over a year.

Salmonellosis – The Dalles, Oregon, 1984

Salmonellosis is the second most common foodborne illness [6], and contaminated food (most often poultry) is the principal route of disease transmission [7]. Salmonellosis manifests as acute gastroenteritis with fever. Occasionally more severe manifestations occur, especially in the very young or elderly.

In 1984, two large cohorts of *Salmonella* cases occurred in The Dalles, Oregon. The size and nature of this outbreak initiated a criminal investigation. The cause only became known when the Federal Bureau of Investigation (FBI) investigated a nearby cult (Rajneeshees) for other criminal violations [8]. In October 1985, a vial containing a culture of *Salmonella* Typhimurium was discovered by authorities in the Rajneeshee clinic laboratory [9]. This strain was indistinguishable from the outbreak strain as isolated from food items and clinical specimens; records were found documenting its purchase prior to the outbreak.

Public health authorities do not normally consider a foodborne salmonellosis outbreak as deliberate. Atypical events associated with this outbreak led to the realization that it was different. Two waves of cases occurred, from 9–18 September, and 19 September–10 October 1984. Health authorities first received illness reports on 17 September. Case interviews by health officials associated patronage of two restaurants in The Dalles with illness, primarily with eating food items from salad bars. *S*. Typhimurium isolates were then obtained from clinical specimens [10]. As gastroenteritis cases occurred in increasing numbers, health authorities closed all salad bars in The Dalles on 25 September.

An extensive investigation was conducted by health officials. Confirmed cases were identified microbiologically by stool culture of *S*. Typhimurium, or clinically. *S*. Typhimurium was isolated from 388 patients. In 4 years before the outbreak, only eight isolates of *S*. Typhimurium were collected by the local health department. Salmonellosis cases had not been reported before August. Eventually, 751 salmonellosis cases were identified, ranging from newborns to 87 years old, with at least 45 hospitalizations. Most cases were associated with dining in 10 area restaurants.

Public health authorities obtained comprehensive food histories from those ill, interviewed restaurant employees, and collected stool samples. The state public health laboratory serotyped *Salmonella* isolates, and performed antibiotic-susceptibility testing. They sent samples of isolates to the Centers for Disease Control and Prevention (CDC) for further characterization, where the outbreak strain was compared with national human and veterinary isolates. Sanitarians inspected restaurants, and collected and analysed tap water. The local health department and the US Department of Agriculture (USDA) investigated distributors and suppliers of foods used in these restaurants. None was found to have contaminated food, nor was there a common supplier for the implicated restaurants.

The source of this outbreak was a puzzle. Epidemiological analysis revealed not a single, but multiple suspect food items as the cause of the restaurant patrons' illness. Intentional contamination

of the salad bars is consistent with this epidemiological pattern. Eventually, two cult members were arrested and served federal prison terms. Despite the success of the restaurant-associated bioterrorism by the commune, the publicity and subsequent legal pressure caused the Rajneeshees to abandon their plan to infect the community during an election.

Shigellosis – Dallas, Texas, 1996

Between 29 October and 1 November 1996, twelve clinical laboratory workers at the St. Paul Medical Center in Dallas developed severe acute diarrhoeal illness as a result of eating muffins and doughnuts left in their break room on 29 October. *Shigella dysenteriae* type 2 was cultured from the stools of eight patients. This was an uncommon strain of *Shigella*, and had not been reported as an outbreak source since 1983. Another individual became ill from pastries brought home by a laboratory worker, and also had a proven *S. dysenteriae* type 2 infection. Five patients were treated in emergency departments and released; four were hospitalized [11].

Epidemiologists interviewed 45 laboratory employees. An anonymous email sent from a supervisor's computer invited workers to eat pastries in the laboratory break room. The supervisor was away from the office when the email was sent, and the break room could only be accessed using a numerical security code. A commercial bakery prepared the pastries, but no other cases were reported in the community. Those ill reported eating a pastry on 29 October between 7:15 am and 1:30 pm. Diarrhoea onset for ill laboratory workers occurred between 9:00 pm that day and 4:00 am on 1 November. The mean incubation period was 25 h and diarrhoea was preceded by nausea, abdominal discomfort, and bloating. Everyone who ate a muffin or doughnut became ill (100% attack rate). No increased risk for illness was found associated with food eaten or beverages consumed from the break-room refrigerator, the hospital cafeteria, or attendance at any social gathering.

Examination of the hospital laboratory storage freezer revealed tampering of reference cultures of *S. dysenteriae* type 2. The stored cultures should each have contained 25 porous beads impregnated with microorganisms, but the *S. dysenteriae* type 2 vial had only 19 beads. Laboratory records indicated that the vial had been unused. *S. dysenteriae* type 2 was isolated from the muffin specimen, and from the stools of eight patients. Pulsed-field gel electrophoresis revealed that reference culture isolates were indistinguishable from each other, but differed from two non-outbreak *S. dysenteriae* type 2 isolates obtained from other Texas counties during that time.

Anthrax – USA 2001

On 4 October 2001, a case of inhalational anthrax was reported in a 63-year-old male in Florida [12]. Public health and government authorities initially announced this individual had probably contracted the illness by hunting [13]. While two other cases occurred in Florida, a fourth case of anthrax, via cutaneous exposure, was identified in a female employee at NBC news in New York City (NYC) [14]. Investigators then realized that exposures had occurred from anthrax-containing letters placed in the mail. On 15 October, a Senate Majority Leader received an anthrax-containing letter, which led to the closure of the Hart Senate Office Building in Washington, DC. [15] By the end of the year, anthrax-laden letters placed in the mail had caused 22 cases of anthrax [11 inhalational (all confirmed), and 11 cutaneous (7 confirmed, 4 suspected)] and five deaths, mostly among postal workers and those handling mail [16, 17]. A twelfth case of cutaneous anthrax related to these mailings occurred in March 2002 in a Texas laboratory where anthrax samples were processed [18].

Accidental release of biological agent

The following case study documents the historic events after the accidental release of *B. anthracis* in the former Soviet Union during the 1970s. The former Soviet Union had a massive state-sponsored BW programme [19]. This account places emphasis upon the terrifying dangers to innocent populations from the deliberate development of biological weapons.

Anthrax – Sverdlovsk, Soviet Union, 1979

In April and May 1979, an unusual anthrax epidemic occurred in Sverdlovsk in the Soviet Union (now Ekaterinburg, Russia). This was the largest historical documented outbreak of human inhalational anthrax, with 66 deaths [20]. Soviet authorities initially claimed it was gastrointestinal anthrax. Gastrointestinal anthrax is an uncharacteristic clinical manifestation from ingestion of *Bacillus anthracis* spores, occasionally reported in former Soviet

Union republics [21]. Years later, when a joint team of Soviet and Western physicians and scientists re-examined case history and autopsy results, it became apparent that inhalational anthrax had caused the outbreak. The distribution of human and animal cases indicated that the disease occurred within a very narrow geographical zone (4 km in length for human exposures, 40 km for animals), and had originated in Sverdlovsk. Taking historical meteorological data into account this demonstrated a point of origin at a military microbiological facility, Compound 19, and that the event probably occurred on 2 April 1979.

An emergency commission established by health authorities around 10 April 1979 directed public health response measures. Sverdlovsk city hospital began triage response by 12 April. Separate areas were designated for screening suspected cases, treating non-systemic cutaneous anthrax, intensive care, and autopsy. Anthrax illness was not known to be transmitted from person-to-person. Officials placed the deceased in coffins containing chlorinated lime and buried them in a discrete area of the city cemetery. They recruited hospital and factory-worker teams to visit homes of suspected and confirmed cases throughout the city. These teams conducted medical interviews, dispensed tetracycline as a prophylactic antibiotic, disinfected kitchens and patient sickrooms, and collected meat and environmental samples for microbiological testing. Local fire brigades washed trees and building exteriors in the section of the city where most cases resided. Stray dogs were shot, and some unpaved streets paved. Posters and newspaper articles warned of the risk of anthrax from either uninspected meat or contact with sick animals. Meat shipments entering the city were examined; uninspected meat was embargoed and burned. In mid-April, 1979, the state started a voluntary anthrax immunization programme for healthy individuals aged 18–55 years in the part of the city where most cases lived. Of 59 000 people eligible to receive anthrax vaccine, about 80 % were vaccinated at least once.

Natural outbreaks that mimic deliberate epidemics

Although the following are examples of naturally occurring outbreaks, they provide epidemiological clues that should raise an index of suspicion of an intentional outbreak. These naturally occurring outbreaks share features with intentionally generated outbreaks. Subsequent to the 1999 West Nile virus (WNV) outbreak in NYC, suggestions were made that a biological weapon had been released covertly by Iraqi operatives. These allegations occurred because documentation existed that: the CDC had provided Iraq with various biological agents from 1984 to 1993, including *Yersinia pestis*, dengue and WNV [22]; the American Type Culture Collection (ATCC) had shipped *C. botulinum* and *Aspergillus* cultures [23]; and the government of Iraq was known to have had a covert biological weapons programme [24]. Similar allegations of the covert use of a biological weapon were made during the 1999–2000 Kosovo tularemia outbreak.

West Nile virus, New York City, 1999

An unusual arboviral encephalitis outbreak was recognized in NYC in August, 1999. On 23 August, an infectious disease physician from a Queens hospital contacted the NYC Department of Hygiene and Mental Health (NYCDOHMH) to report two encephalitis patients. NYCDOHMH then conducted a city-wide investigation that revealed a cluster of six encephalitis patients, five having profound muscle weakness, and four requiring respiratory support. Initial clinical sample tests from these patients by the CDC revealed that they were positive for Saint Louis encephalitis, on 3 September. Additional encephalitis cases ensued. As eight of the earliest cases were residents of a 2-square-mile area in Queens, aerial and ground applications of mosquito pesticides began in northern Queens and South Bronx on 3 September [25].

Active encephalitis surveillance began in NYC on 30 August, and in nearby Nassau and Westchester counties on 3 September. A clinical case definition was used. Before and during this outbreak, an observed increase in bird deaths (particularly crows) was noted in NYC [26]. Tissue specimens from birds in the Bronx Zoo were analysed by the CDC, which revealed on 23 September that the virus was WNV-like in genetic composition [27]. Up to that time, WNV had never been isolated in the Western hemisphere.

Concurrently, brain tissue from three NYC encephalitis case deaths tested positive for WNV at the University of California at Irvine. As of 28 September 1999, 17 confirmed and 20 probable cases had occurred in NYC, Nassau, and Westchester counties, with four deaths. Onset dates were from 5 August to 16 September, and the median age of

the case-patients was 71 years (range 15–87 years). By 5 October, the number of laboratory-positive cases increased to 50 (27 confirmed and 23 probable). The NYCDOHMH established emergency telephone hotlines on 3 September, with 130 000 calls received by 28 September. They distributed over 300 000 cans of DEET-based mosquito repellent citywide through local firehouses, and 750 000 public health leaflets with information on protection from mosquito bites. They provided public health messages by radio, television, and via the internet. A seroprevalence survey later determined that about 100 asymptomatic infections and 30 WNV fever cases occurred for each WNV encephalitis case in the NYC area [28].

Tularemia, Kosovo, 2000

After a decade of political crises and warfare, a large outbreak of tularemia occurred in Kosovo in 1999–2000. No cases of tularemia had been reported in Kosovo since 1974 [29]. By April 2000, 250 suspected cases had been identified, spread nationwide, with most cases in the western area where ethnic Albanians resided [30].

Unusual outbreaks of zoonoses or vector-borne disease may occur readily in war-torn or crisis-afflicted regions that have previously been free of these diseases. Speculation may arise that these epidemics have been caused intentionally [31]. Many biological agents are zoonotic pathogens, including the category A BW pathogen, *Franciscella tularensis* [32]. Unsubstantiated statements by the head epidemiologist at the Kosovo Institute of Public Health concerning unidentified ampoules and powders found near various wells added to a perception of BW use by Serbian forces.

F. tularensis biovar *tularensis* (type A), found primarily in North America, is highly pathogenic for humans and has been developed as a biological weapon. Disease progression often follows an acute and severe course, with pneumonitis prominent. Tularemia is naturally transmitted to humans through skin lesions of those handling diseased rabbits [33] or ingesting contaminated water [34] or food [35], from bites of infectious arthropods [36], or inhalation of infective dusts [37]. *F. tularensis* biovar *holoarctica* (type B) is less pathogenic and found throughout the entire northern hemisphere [38]. To further complicate matters, in 1998, type A tularemia had been documented in arthropod populations in the nearby Slovak Republic [39].

The United Nations Mission in Kosovo asked the World Health Organization (WHO) to assist Kosovar health authorities. Teams of public health personnel collaborated in epidemiological, environmental and microbiological field and laboratory investigations [40]. They uncovered tularemia cases using prospective surveillance and retrospective hospital review of a pharyngitis and cervical lymphadenitis syndrome. They examined and interviewed patients, took blood samples from suspected cases, and prescribed antibiotics as appropriate. Rural villagers reported an increase in the numbers of mice and rats in the summer of 1999. A causal association was suspected between the increased population density of rodents and human tularemia cases.

The investigators conducted a matched case-control study with paired households in villages containing the most reported cases. All suspected cases provided blood samples, and completed questionnaires on household food consumption, water supply, presence of rodents, and condition of wells and food preparation and storage areas. The investigators performed well-water sampling and rodent collection and analysis.

By 30 June 2000, over 900 suspected cases of tularemia were discovered, with 327 confirmed as serologically positive. The earliest onset of reported symptoms in the confirmed cases was October 1999, with an epidemic peak in January 2000. Confirmed cases were identified in 21 of 29 Kosovo municipalities. Risk factors for case households included rodent faeces in food preparation and storage areas, and large numbers of field mice observed outside the house. Of the field samples collected, the positive antigen for *F. tularensis* was detected in field mice and rats.

Potential epidemiological clues to a deliberate epidemic

In the event of a deliberately caused epidemic, the number of casualties may be small, and therefore unrecognized as intentionally infected. Moreover, individuals may disperse throughout the country before they become ill and seek medical care. Care providers should be aware of potential clues that may be 'red flags' that something unusual has occurred. While these clues may occur with natural outbreaks and do not necessarily signal a deliberate attack with a biological agent, they should heighten one's

index of suspicion that an unnatural event has occurred [41, 42].

Clue no. 1 – A highly unusual event with large numbers of casualties. Naturally spread illness may cause a large group of ill individuals. However, large outbreaks should merit particular attention, especially when there is no plausible natural explanation for the cause. The 1984 salmonellosis outbreak in The Dalles, Oregon, is an example of this.

Clue no. 2 – Higher morbidity or mortality than is expected. A higher morbidity or mortality than typically observed for a particular disease may provide a clue to an unusual event. The biological agent may have been altered for greater pathogenicity, or individuals could be exposed to a higher inoculum than would be natural. Additionally, if the disease should be sensitive to certain antibiotics, but displays resistance, then possibly resistance was genetically engineered. The cases of anthrax at Sverdlovsk had high mortality. A high mortality could be seen with gastrointestinal anthrax, which the government claimed to be the cause at the time. Linking the pathological findings of respiratory disease with the high mortality made inhalational anthrax more likely.

Clue no. 3 – Uncommon disease. Many infectious diseases have predictable distributions based on environmental, host, and vector factors. One should consider a disease outbreak uncommon for a geographical area as having been unnaturally spread. Concern should be heightened if the disease requires a competent vector for spread, and that vector is not thought to be present. Natural outbreaks have in fact occurred in novel geographical locations. Examples include the appearance of West Nile virus (WNV) in NYC in 1999 [43] and also bubonic plague cases in NYC in 2002 [44]. The 1996 outbreak of *Shigella* in Dallas was unusual since the strain was uncommon, there was no current research being conducted at the hospital, there were no other outbreaks in the community at the time, and no identifiable contamination at the manufacturing facility. The WNV outbreak constituted a true emerging infection, as the disease became established in a new location, while the plague cases were simply imported by out-of-state residents. It is important to at least consider, in these situations, whether the disease is natural or deliberate.

Clue no. 4 – Point-source outbreak. In an intentional event, dates of onset would probably depict a point-source outbreak curve [45]. This shows a fairly quick rise in cases, a brief plateau, and then an acute drop. The curve might be somewhat compressed due to the individuals being exposed more closely in time (i.e. seconds to minutes of each other) from an aerosol release, compared with individuals becoming ill after eating a common food over a period of minutes to hours. The inoculum may also be greater than that typically seen with natural spread, thus yielding a shorter than expected incubation period. The 1979 anthrax epidemic in Sverdlovsk was a point-source release. In addition, the *Shigella* outbreak in Texas demonstrated a classical point-source curve. The US anthrax mailings presented a different kind of point-source outbreak. What made that situation unusual was that the actual point sources (the letters) were travelling through the mail system. This led to an outbreak pattern with individual cases spread over time and distance (multiple states).

Clue no. 5 – Multiple epidemics. Multiple perpetrators in collaboration could release a single biological agent at various locations, or even multiple agents from multiple locations. Hence, should simultaneous epidemics occur at different locations, with the same or multiple organisms, one should consider an unnatural source. The 1984 salmonellosis outbreaks in The Dalles, Oregon were a series of multiple epidemics, as were the illnesses caused in multiple locations by the US anthrax letters. It is also possible that a mixture of organisms with different incubation periods could be used to spread disease, thus causing serial outbreaks of different diseases in the same population over time.

Clue no. 6 – Lower attack rates in protected individuals. This clue applies to military populations, and also to those in buildings with filtered air supply. For example, if a group wore military-oriented protective posture (MOPP) gear or other devices that protect airways (such as high-efficiency particulate air (HEPA)-filtered masks or stayed in a HEPA-filtered tent), and had lower rates of illness than unprotected groups in the same geographical area, this should prompt consideration of exposure to an aerosolized agent.

Clue no. 7 – Dead animals. Animals have been used historically as sentinels of human disease – one example is canaries used in coal mines to detect noxious gases. Many biological agents that could be intentionally used are zoonotic. A regionalized animal die-off may provide a clue that something has been released that might infect humans. This phenomenon was observed during the WNV encephalitis outbreak in NYC in 1999, when many local crows, along with exotic birds at the Bronx Zoo, died [46, 47]. Also, in the Sverdlovsk outbreak, there were reports of dead sheep downwind from the source.

Clue no. 8 – Reverse spread. The typical pattern with a zoonosis is disease occurring in a susceptible animal population, being followed by cases in humans. When Sin Nombre virus first surfaced in the desert southwest of the United States [48], it followed a surge in the population of field mice (*Peromyscus maniculatus*), virus spread amongst the mice, and subsequent excretion of virus in their urine [49]. Humans in close proximity to the mice then became infected. Should human disease precede animal disease or human and animal disease occur simultaneously, one should consider unnatural spread.

Clue no. 9 – Unusual disease manifestation. As over 95% of anthrax cases worldwide are cutaneous, even one case of inhalational anthrax should be considered an unnatural event until proven otherwise. It is illogical to suggest that 66 deaths resulting from the outbreak of inhalational anthrax in Sverdlovsk in 1979 was from a natural source. The same applies to cases of inhalation and cutaneous anthrax occurring in multiple states at the same or similar times. Pneumonic plague cases may be suspected if most cases are the bubonic form. Since pneumonic tularemia (e.g. as had occurred in the 2000 natural outbreak in Martha's Vineyard, Massachusetts) [50] could also result from an aerosol release of *F. tularensis*, this manifestation should also be suspected [51].

Clue no. 10 – Downwind plume pattern. It is useful to plot locations where cases occur on a geographic grid or map. If affected cases are clustered in a downwind pattern, an aerosol release should be considered. This was recognized in the 1979 anthrax outbreak in Sverdlovsk, and was instrumental in determining that the cases were caused by aerosol rather than a contaminated food source [52].

Clue no. 11 – Direct evidence. A perpetrator leaving evidence would make determining the intentional cause of illnesses easier. The evidence could be a letter filled with anthrax spores, as in 2001 in the United States [53], the discovery of a spray device, or another vehicle used for the agent's spread, such as contaminated food, as with *Salmonella* in Oregon and *Shigella* in Texas. Samples from a suspect device can be compared with those from victims to verify that they are the same strain of organism.

REVIEW OF EPIDEMIOLOGICAL CASE STUDIES AND APPLICATION OF EPIDEMIOLOGICAL CLUES

Case review of 1984 salmonellosis outbreak

Biological agent: *Salmonella* Typhimurium

Potential epidemiological clues: 1, 4, 5, 11

Review: One commune member admitted placing bacterial culture in salad dressing; it is unknown if other food items were contaminated. More than one year after the outbreak had occurred, the law enforcement investigation revealed intentional restaurant food contamination by the Rajneeshees.

In 1984, public health and law enforcement authorities lacked cooperative protocols and were probably uncomfortable sharing information. Public health and the law enforcement team in Oregon did cooperate, as evidenced by a public health laboratory official who accompanied the FBI. This individual discovered the *S.* Typhimurium culture, which may have otherwise gone unnoticed. Today, an outbreak of this magnitude would lead to the initiation of a joint inquiry and investigation by public health and law enforcement, and the cause should be identified more rapidly.

These events demonstrate why mutual cooperation is important during joint public health and law enforcement investigations. This outbreak also illustrates that mode of spread of disease influences the evaluation of an outbreak's origins. When a foodborne disease does not occur naturally, an unlikely vehicle may be responsible. Moreover, when different restaurant locations are involved, one would expect that a central supplier shipped a contaminated product to the various restaurants. In this case, a coordinated shipping of a contaminated product did not occur, which should have indicated deliberate contamination.

Case review of 1996 shigellosis food poisonings

Biological agent: *Shigella dysenteriae* type 2

Potential epidemiological clues: 3, 4, 11

Review: A robust epidemiological link existed between cases, the uneaten muffin, and the laboratory's stock culture of *S. dysenteriae* type 2. The pathogen was uncommon. The hospital had not conducted research with this microorganism, so no occupational risk of infection existed. No health departments reported concurrent outbreaks of *S. dysenteriae* type 2. Contamination of pastries during commercial production was doubtful – *Shigella* will not survive cooking temperatures. Therefore, contamination by a food service worker during food preparation would have had to occur subsequent to baking.

When the epidemiological report was published, it was hypothesized that someone had removed the laboratory culture of *S. dysenteriae* type 2 from the freezer, possessed the laboratory skills to culture the microorganism and inoculate pastries, and accessed the locked break room [22]. On 28 August 1997, investigators indicted a laboratory technician who had access to the laboratory culture stocks (and had also previously used biological agents against a boyfriend) on three charges of tampering with a food product, and infecting 12 co-workers with *S. dysenteriae* type 2. She was eventually sentenced to 20 years in prison [54].

The match of clinical, food and laboratory isolates, along with laboratory culture records, helped to provide the epidemiological link. Only someone having direct access to the laboratory culture could have committed this 'biocrime', and that person was eventually apprehended.

Case review of the 2001 anthrax mailings

Biological agent: *Bacillus anthracis*

Potential epidemiological clues: 3, 5, 9, 11

Review: The national response to these events was enormous in scope. Unprecedented public health and law enforcement investigations ensued, involving thousands of investigators from federal, state, and local agencies. The CDC and FBI collaborated to conduct public health and criminal investigations [55]. Public health surveillance for unidentified or unreported anthrax cases associated with the mail intensified, severely straining public health capacity [56, 57]. The Laboratory Response Network [58], a network connecting local and state public health laboratories with national public health and military laboratories, developed into a lead resource for ruling out, and identification of, a potential biological attack [59]. High-resolution molecular subtyping of *B. anthracis* determined that the mail-related isolates were indistinguishable and probably came from a single source [60]. Postal workers and others handling mail were shown to be at risk from the anthrax-containing letters [61] and contaminated postal machinery [62], so environmental sampling [63], cleaning [64] and protective measures, along with antibiotic prophylaxis were instituted [65]. Similar steps were taken following discovery of the anthrax spore-laden envelope opened in the Senate Office Building [66]. Monitoring of this population provided invaluable information concerning anthrax exposures and efficacy of prophylaxis [67].

Anthrax was known to be an occupational hazard to industrial workers in the United States before Robert Koch isolated *B. anthracis* in 1877 [68]. As of summer 2006, the perpetrator of the anthrax mailings has not been apprehended by law enforcement authorities. The anthrax mailings greatly influenced public perception of vulnerability to biological attack. In the month following public notification of bioterrorism-related anthrax cases, the CDC responded to over 11 000 phone calls [69]. State and local health departments also received continuous queries from health- care providers requesting clinical information to rule out anthrax, the media, and countless reports of 'white powder' incidents with demands for instant *B. anthracis* determination [70]. In states where anthrax cases had occurred, these demands were exacerbated by requirements for anthrax exposure assessments for postal workers, patients' workplace and home environments, distribution of pharmaceuticals, and exhaustive state-wide prospective and retrospective anthrax-syndromic surveillance case review and reporting [71].

On 31 January 2002, as a direct result of the anthrax mailings, the federal government made available $1.1 billion in funding to states for bioterrorism preparedness [72]. Disease detection and notification efforts have changed dramatically since the anthrax mailings of 2001. Automated laboratory reporting via the National Electronic Disease Surveillance System (NEDSS) [73] and automated hospital syndromic surveillance reporting [74] to public health agencies in many states and large cities have been implemented. Continuing efforts to

strengthen the public health workforce should enable better detection, response, and management of a future bioterrorism crisis [75].

Among the epidemiological 'lessons learned' from the anthrax mailings is that an enhanced index of suspicion is necessary for unusual manifestations of diseases associated with bioterrorism.

Case review of the 1979 Sverdlovsk anthrax release

Biological agent: *Bacillus anthracis*

Potential epidemiological clues: 1, 2, 3, 4, 7, 9, 10

Review: In the absence of confirmatory information of an aerosol anthrax release, a phenomenal public health response was mounted by health officials. Recent research has estimated that about 14% more deaths could have occurred in Sverdlovsk without public health intervention that included antibiotic distribution and vaccination [76]. The Soviet military concealed facts that would have aided diagnosis and treatment of victims. It is possible that more individuals were ill and recovered, or died, than records indicate [77]. Ambulance medical personnel often made an initial case diagnosis of pneumonia [78].

The Soviet government confiscated patient records and autopsy reports from the hospital. These records could have provided invaluable medical intervention information for those patients that survived. Combined with the absence of an epidemiological investigation, this was a serious loss of biological defence information against aerosolized anthrax [79]. Significant information about anthrax prophylaxis and treatment was later obtained from Soviet physicians, who, at their own risk, had taken tissue samples and records home. From their work we understand that the incubation period for inhalational anthrax may be as long as 2 months, and that an antibiotic course of 5 days' duration probably prolonged the incubation period for illness. Molecular analysis of tissue samples collected from 11 victims and retained by Sverdlovsk physicians indicated that they had been exposed to different *B. anthracis* strains [80]. This contradicts the claim of a single naturally occurring source for the outbreak, and points towards the release of a BW anthrax formulation from Compound 19.

Among the epidemiological 'lessons learned' from this event is that retrospective pathological findings from victims, weather patterns, and geographic mapping can assist in determining whether an outbreak was intentional or not. The public health personnel in Sverdlovsk probably instituted effective preventive measures before they knew exactly what caused the illness. They used information from cases to determine possible exposure routes, and once the disease agent was determined, they provided prophylactic antibiotics and vaccination, and began precautionary environmental measures.

Case review of the 1999 West Nile virus outbreak

Biological agent: West Nile virus

Potential epidemiological clues: 1, 2, 3, 7

Review: A magazine article claimed that WNV had been developed as a biological weapon by Cuba and Iraq [81]. Although it may be impossible to disprove completely such a claim, it is more difficult to substantiate. The appearance of WNV in NYC in 1999, and its subsequent spread throughout the United States, was probably a natural occurrence.

Within its normal geographic area of distribution in Africa, West Asia, and the Middle East, birds do not normally show symptoms when infected with WNV [82]. Migrant birds from this part of the world are thought to cause occasional WNV epidemics in Europe [83, 84]. An epizootic that results in the deaths of large numbers of birds may represent introduction into a new population or a new more virulent strain of a virus.

WNV is primarily transmitted by *Culex pipiens* mosquitoes [85], which also contributed to its subsequent spread in the United States [86]. This prompted nationwide mosquito population surveillance. Genetic testing revealed that the virus was 99% identical to one isolated in 1999 from a goose in Israel [87]. Potential routes for introduction of this virus include importation of WNV-infected birds, mosquitoes, or ill persons. The WNV-prevalent area of NYC included two large international airports [88]. In WNV encephalitis patients, computer-assisted tomography often revealed pre-existing lesions and chronic changes in brain tissue [89], suggestive of a greater susceptibility to deleterious outcome in the elderly.

This outbreak emphasized the important relationship between veterinarians, physicians, and Public Health in disease surveillance, and that uncommon pathogens must be considered [90]. Among the epidemiological 'lessons learned' from the 1999 WNV outbreak was the example of a typical disease pattern

seen with a natural epidemic, occurring first among birds, followed by cases of human illness. With the establishment of WNV in indigenous North American mosquito vectors, the virus has spread and become endemic to the continent. Importantly, the origin of outbreaks fitting some clues for a biological attack (e.g. a new disease in a geographic region), cannot be determined without extensive investigation. Emerging diseases, both new to a region like WNV, and a totally new pathogen (e.g. SARS), have occurred in the last decade. Regardless of outbreak origin, the epidemiological methods remain the same.

Case review of the 2000 Kosovo tularemia outbreak

Biological agent: *Francisella tularensis*

Potential epidemiological clues: 1, 3, 5, 9

Review: Clinical and serological evidence indicated that a tularemia outbreak occurred in Kosovo during October 1999 to May 2000. The case-control study indicated foodborne transmission, based on the associations of illness and large numbers of rodents in the household environment, rodent contamination of food storage and preparation areas, and eating uncooked foods. Contaminated water probably contributed to the outbreak.

The investigators also considered intentional spread of tularemia. They determined through initial field investigations that a widespread natural event occurred, and probably resulted from the unusual environmental conditions in war-torn Kosovo. Ethnic Albanians with limited economic resources in rural farming villages were most affected. They had fled bombing and Serbian reprisals of the spring of 1999. Upon return to their villages, refugees discovered destroyed and ransacked homes, unprotected food storage areas, unharvested crops, damaged wells, and a population explosion of rodents. Ignorance of infection and lack of hygienic measures contributed to a food-borne outbreak in the population [77]. These factors resulted in conditions favourable for epizootic spread of tularemia in rodents and widespread environmental contamination with *F. tularensis*, since this organism can survive for prolonged periods in cold, moist conditions. A natural decrease in the rodent population attributed to the cold winter, food shortages and the disease itself probably combined to end the zoonoses [77]. The largest European tularemia outbreak previously reported had occurred in the former Soviet Union during the Second World War [82].

The epidemiological 'lesson learned' from the Kosovo tularemia outbreak is that war provides a fertile ground for the re-emergence of diseases as well as potential concealment for the use of a BW agent.

Epidemiological assessment tool

Grunow & Finke [29] developed an epidemiological assessment tool to identify or rule out BW in the event of an unusual infectious disease outbreak, using specific criteria. The assessment tool was developed to permit a retrospective epidemiological analysis of new or repeatedly occurring 'unusual' epidemics and the politico-military, socioeconomic, medical, epizootological, epidemiological and environmental situation in the outbreak region; make informed statements on the probability of a natural or artificial outbreak by weighting the criteria; and conduct a retrospective analysis of earlier epidemics and suspected uses of BW agents using available data.

This evaluation scheme described two types of evaluation criteria: conclusive and non-conclusive. Conclusive criteria include the proven identification of the cause of illness as a BW agent, or proof of the release of an agent as a biological weapon. Confirmatory information is unnecessary. With non-conclusive criteria, the greatest significance (assignment of higher weighting factors) is credited to the existence of a biological threat or risk, special aspects of a biological agent, a high concentration of biological agent in the environment, and epidemic characteristics. Each assessment criterion is assigned a varying number of points dependent upon the presence of that criterion and its tendency towards demonstrating retrospectively that a BW agent had been used.

Using the tularemia outbreak as an example, the following are the 11 Grunow & Finke non-conclusive criteria. The first two criteria are characteristics derived from the political, military and social analysis of the region; the subsequent three criteria describe features of the pathogen; and the final six criteria represent epidemiological and clinical characteristics of the epidemic.

- *Biorisk*. Are BW agents available, with the means for distribution, and the will to use them? Or can an outbreak be explained by natural biological hazards, or the changes incurred by military

conflict? (A natural occurrence of tularemia in Kosovo, even without a previous outbreak, must be considered.)

- *Biothreat*. Does a biological threat exist with a group possessing a BW agent and threatening to use it? (No evidence for this existed in Kosovo.)
- *Special aspects*. Is there plausible evidence of deliberate pathogen manipulation? (This could not be determined in Kosovo. No bacterial cultures were created due to lack of resources and fear of laboratory transmission.)
- *Geographic distribution*. Is the disease's geographic distribution probable given its locale? With the advent of a non-endemic pathogen, a thorough evaluation should include epidemiological, epizootic, ecological, microbiological and forensic analysis. (A 25-year absence of reported tularemia did not eliminate the potential natural occurrence of an epidemic.)
- *Environmental concentration*. Is there a high environmental concentration of the pathogen? (The almost exclusive occurrence of oropharyngeal tularemia in Kosovo probably indicated ingestion of a high number of bacteria that could occur through food or water contamination. *F. tularensis* was not found in drinking water and soil, but was discovered in rodent vectors.)
- *Epidemic intensity*. Is the course of illness relative to disease intensity and spread in the population expected in naturally occurring illness? (Since tularemia was absent in Kosovo prior to the epidemic, this was considered to be an unusually intensive outbreak.)
- *Transmission mode*. Was the path of disease transmission naturally occurring? (Evidence existed in Kosovo for known disease transmission, but the appearance of a naturally occurring epidemic alone does not rule out deliberate use of a biological agent.)
- *Time*. Was the calendar time of the epidemic abnormal? (This epidemic began in October 1999, peaked in January 2000, and ended in May. This is a characteristic seasonal pattern for a naturally occurring European tularemia epidemic.)
- *Unusually rapid spread*. Was the spread of the epidemic unusually rapid? (It was unusual in that within a brief time, tularemia appeared throughout almost the entire Albanian territory of Kosovo.)
- *Population limitation*. Was the epidemic limited to a specific (target) population? (If certain individuals had forewarning of a BW attack, they might protect themselves, as compared to naive target populations. The Serbian population was not spared, and poor hygiene and living conditions may have facilitated the spread of disease in the ethnic Albanian population.)
- *Clinical*. Were the clinical manifestations as expected for the disease? (With the Kosovo outbreak, clinical diagnosis was complicated by the simultaneous appearance of mumps and tuberculosis in the population. Oropharyngeal tularemia is less common than the ulceroglandular form, but could be explained by oral transmission.)

We used the Grunow & Finke epidemiological assessment procedure in the Table to evaluate the case studies presented. Some artificial constraints were placed upon the analysis to use this assessment tool uniformly for all events. We used only the non-conclusive criteria for this evaluation. Non-conclusive evaluation criteria would always be used during the course of an epidemiological investigation. With the exception of the 2001 anthrax mailings, none of the outbreaks described had been positively identified as having been caused by a biological agent until some time after the event(s) had occurred. Therefore, we applied the non-conclusive criteria evaluation tool, considering all of the information presented for each case study, and deliberately excluded knowledge about the deliberate use of a biological agent.

The use of the non-conclusive criteria in this manner led to novel observations. In their work, Grunow & Finke provide cut-off scores for these criteria with respect to the assessment of the likelihood of the use of a biological weapon: unlikely (0–33% confidence) = 0–17 points; doubtful (18–35% confidence) = 18–35 points; likely (67–94% confidence) = 36–50 points; highly likely (95–100% confidence) = 51–54 points. Based upon this scale and our scoring, only the anthrax mailings in 2001 would be considered as highly likely to have been caused by a BW agent. The Sverdlovsk anthrax outbreak is considered likely to have been caused by a BW agent. Neither the 1984 *Salmonella* nor the 1996 *Shigella* outbreaks, both caused by common foodborne pathogens, were discernible as deliberate epidemics using these criteria. The other case scenarios examined were categorized as doubtful to have been deliberately caused.

Although subjective, this exercise underscores the challenge epidemiologists have in determining whether or not a deliberate outbreak has occurred,

Table. *Epidemiological assessment evaluation of case-study outbreaks and model scenario*

Non-conclusive criteria	Assessment (possible points)	Weighting factor	Maximum no. of points	1979 anthrax Sverdlovsk	1984 Salmonella Oregon	1996 Shigella Texas	1999 WNV NYC	1999 tularemia Kosovo	2001 anthrax USA	Model scenario for deliberate epidemic
Biorisk	0–3	2	6	4	6	0	6	2	6	2
Biothreat	0–3	3	9	0	0	0	6	3	6	3
Special aspects	0–3	3	9	6	3	6	0	0	9	6
Geographic distribution	0–3	1	3	3	2	2	3	3	3	3
Environmental concentration	0–3	2	6	6	0	0	4	4	6	6
Epidemic intensity	0–3	1	3	3	3	3	3	3	3	3
Transmission mode	0–3	2	6	6	4	0	2	2	6	6
Time	0–3	1	3	3	1	1	1	0	3	1
Unusually rapid spread	0–3	1	3	3	3	3	3	1	3	3
Population limitation	0–3	1	3	1	0	3	0	0	3	1
Clinical score	0–3	1	3	3	0	1	1	1	3	3
Total			54	38	22	19	29	19	51	37

unless evidence is found that points to such a deliberate event or someone claims responsibility. Basic epidemiological principles, including those necessary for disease recognition, to determine the occurrence of an unnatural event, and for outbreak investigation, are the foundation of infectious disease response and control. Public health authorities must remain vigilant to respond quickly and appropriately to any infectious disease event.

Management of outbreaks

Control measures to manage an infectious disease outbreak should be implemented in a timely and appropriate manner [91]. Such measures are influenced by the ongoing epidemiological investigation and its eventual findings, as well as by many of the non-conclusive criteria identified in the Grunow–Finke analysis. Actions taken to control an outbreak are determined by the information available to public health authorities at the time that they are implemented. These steps are often modified as additional information becomes available during the investigation (e.g. reporting of additional cases in a wider geographical area, or further knowledge gained from case interviews).

It is of primary importance in an outbreak investigation to: find quickly the source of the disease, identify all cases associated with the outbreak, and to prevent additional cases. Additional unreported cases associated with the outbreak may need to be identified. Those cases of disease that have already been reported to health authorities rely upon the effectiveness of the existing disease surveillance systems, whether via passive or active surveillance.

If there is the potential for person-to-person transmission of the illness, it is important to identify quickly all those who have been exposed to primary cases. This may be difficult. Additional cases may be far removed in time and place from the point of initial exposure [92]. Many of the diseases caused by bioterrorism agents have low natural incidence rates, and lack of clinician experience with these diseases can impede rapid diagnosis and reporting to public health authorities [93]. An unrecognized index case may delay the outbreak investigation [51].

Upon notification of an unusual case(s) to a healthcare provider or local hospital, a progressive response is taken by local health authorities [94]. Clinical or laboratory findings must be available to confirm that the disease has occurred. An epidemiological and

(if applicable) an environmental investigation is initiated, following the usual steps of case definition, case finding and analysis [95]. The case definition may be modified as additional information about the nature of the outbreak becomes available. A hypothesis about how the disease occurred will be developed. The Grunow–Finke analysis should prove useful in this regard to help determine whether an outbreak might be of deliberate or natural origin.

Notification of suspected and confirmed case(s) is made to the central health agency, and also a request for assistance in the investigation, if required. The central health agency should notify the Department of Health of an investigation concerning a category A pathogen or an infectious disease investigation that could prove of national significance. Additional public health assistance may also be requested. Control measures to stop the outbreak should be established as rapidly as possible, and modified as more information becomes available. Information may need to be communicated through the media to help control the outbreak. Law enforcement personnel will need to be involved in any suspected bioterrorism case as early as possible.

Telephone, facsimile, and electronic notifications may also be sent to all potential disease reporters within the public health agency's jurisdiction, including clinical laboratories [96], veterinarians [97], and medical examiners [98]. In the United States, depending upon the nature and extent of the outbreak, an incident command system (ICS) may be established. This ICS would in turn report to an activated statewide emergency operations centre (EOC). Prophylactic medications or immunizations may need to be requested and supplied through the CDC's Strategic National Stockpile (SNS) of medicine and medical supplies [99]. Deployment and distribution of these medical assets will require additional resource mobilization by state and local governments [100].

There are key points to consider related to outbreak investigation in the era of bioterrorism. The fundamental aspects of outbreak investigation in the setting of a deliberately spread infection and one that is not do not differ significantly. In fact, it is likely that the event will not be known or suspected to be deliberately spread in the early phases of the investigation. However, there are some aspects which would probably differ in how an investigation is conducted, such as engaging law enforcement personnel early on. Indeed, it may be preferable to have law enforcement personnel working side-by-side with public health personnel, especially when it comes to sample collection. Ensuring that samples are collected and transferred with the appropriate chain of custody will ultimately aid law enforcement when the time comes to try the perpetrator.

Another key difference is that since the disease is spread intentionally, the mode of spread may not follow natural epidemiological patterns. The opportunity exists for simultaneous or serial outbreaks, as stated under the potential clues noted above. The unnatural mode of spread could potentially place individuals investigating the outbreak at risk of illness. Therefore, one has to be prudent in protecting oneself and one's personnel. It is also more difficult to know if and when the outbreak has subsided. In short, epidemiologists need to keep an open mind and to expect the unexpected.

Model scenario for deliberately caused epidemic

Many challenges exist for public health agencies to be able to respond to a deliberate epidemic. These may include large numbers of cases having a nondescript illness in its initial manifestation, or highly communicable disease, such as pneumonic plague or smallpox. Neither state health agencies nor hospitals are fully prepared for the possible myriad adverse events surrounding such an event. Bioterrorism response exercises, if conducted properly, will often stress the resources of the hospital or health agency performing the exercise, and its surrounding community. Such exercises will hopefully strengthen the ability to prevent institutional inertia and to better respond should such an event occur. A model deliberate epidemic scenario is presented below.

Day 1 (*the first Saturday in July*) [*8:00 am*]

Scenario: A 52-year-old female enters Metropolitan City hospital A Emergency Department (ED) with a headache, high fever, chills, myalgia, and malaise. The triage nurse records into the chief complaint log: generalized aches and pains, sore throat, congestion, and a temperature of 39·5 °C (103·1 F). The patient claims to have begun feeling ill with backache and headache 4 days previously, and has self-medicated with aspirin and cold medicines. The patient is seen by a physician and routine laboratory tests are ordered. A summer viral upper respiratory infection is suspected. No antibiotics are prescribed. The patient is directed to take anti-pyretics as needed,

drink plenty of fluids, and to return if no improvement occurs within the following 2 or 3 days.

Response: No report of any unusual illness is made to public health authorities.

Day 1 [*3:00 pm*]

Scenario: A 14-month-old female presents to the Metropolitan City hospital B ED with a fever of 38·9 °C (102 F), malaise, and a sore throat. The diagnosis is probable streptococcal pharyngitis. Rapid streptococcal testing is not available, so the parents are instructed to treat their daughter's symptoms with amoxicillin (until the throat culture is available in the next 24 h), children's paracetomol and plenty of fluids.

Response: No report of any unusual illness is made to public health authorities. This case presented at a different venue from the first case, and nothing discerning was noted either by examining clinicians or by notation made into an electronic ED database which is sent to the local health agency every 24 h.

Day 1 [*10:00 pm*]

Scenario: A 71-year-old male visits his personal physician, complaining of fever, weakness, cough, and a temperature of 39·3 °C (102·8 F), and was noted to have cervical adenopathy. The physician questions the patient about his illness. The patient has been ill for 6 days, has experienced weight loss of about 2·3 kg (5 pounds). He does not recall anything particularly unusual, except attending a large sporting event (baseball) in the previous week. The patient is prescribed an antibiotic (levofloxacin) for presumed bronchitis, and referred to a speciality group for investigation for cancer due to the weight loss. Blood samples are taken for full blood count (FBC), chemistry, and bacterial culture.

Response: No report of any unusual illness is made to public health authorities. Since this patient was not seen at a hospital, no electronic surveillance reporting method records the case.

Day 2 (*Sunday*) [*9:00 am*]

Scenario: A 28-year-old female presents to Metropolitan City hospital B ED with neck and head pain, a history of diarrhoea, recent weight loss, chest congestion, and fever of 39·4 °C (103 F). The patient recounts having been immunized against most childhood diseases in her native country. Pneumonia is diagnosed, an antibiotic (azithromycin) is prescribed, and blood specimens are taken for FBC, chemistry, cultures, along with sputum culture. Upon questioning, the patient recalls attending a baseball game during the previous week.

Response: This physician was different from the one who saw examined the first patient. No report of any unusual illness is made to public health authorities. However, due to the combination of fever, chest congestion, and diarrhoea noted on ICD-10 coding, this case is subsequently entered into an electronic ED database which is sent to the local health agency every 24 h.

Day 2 [*8:00 pm*]

Scenario: A 68-year-old woman and her 14-year-old granddaughter present at Metropolitan City hospital A ED with elevated temperatures, bronchitis, and malaise. Patient history reveals that they had a similar onset of symptoms, about 6 days previously. The examining physician suspects that the 68-year-old has pneumonia and a COPD exacerbation, but is puzzled that another family member has similar symptoms. The 14-year-old is diagnosed with bronchitis, prescribed an antibiotic, and returned to her parents. The 68-year-old's illness is severe enough to prompt admission to the hospital. Routine blood samples are taken of both patients, while the 68-year-old has sputum, blood, and urine cultures obtained. The attending physician is concerned about the patient's hypoxaemia, recommends she be monitored in intensive care overnight and asks for an infectious disease consultation. Upon questioning, both patients recall attending a baseball game during the previous week.

Response: The infectious disease specialist examines the newly admitted patient. She makes a mental note of the significant symptoms of the patient, and upon speaking with the ED chief physician, determines that there are similarities between this case, and the ones that presented the previous morning at the hospital. At 5:00 am, she calls the City Public Health Department to discuss these three cases. The City Public Health Department then confers with the state epidemiologist to see if there had been reports of unusual illness elsewhere.

Day 3 (*Monday*) [*8:00 am*]

Response: The state epidemiologist arrives at his office. He is concerned that an outbreak may be occurring, the source of which is as yet unknown. He has recognized the following epidemiological clues as potentially indicative of an unnatural disease event: uncommon disease (clue no. 3), and unusual disease manifestation (clue no. 9). Phone calls made to the area's hospitals have identified the other patients from Metropolitan City hospital B. The hospital laboratories are contacted, and queried about the status of their testing on these patients. All other area hospitals are contacted, and asked to heighten surveillance for similar cases. Clinicians are requested to obtain routine bacterial cultures (blood, urine, sputum, stool) for any potential additional cases. Laboratory testing of all clinical samples from the hospital patients is coordinated with the state health laboratory.

Day 3 [*11:00 am*]

Response: A staff epidemiologist is sent to interview the 68-year-old patient at Metropolitan City hospital A. Other epidemiologists review the ED records from both hospitals and contact the non-admitted patients. The state health veterinarian contacts veterinarians statewide, and learns that an increase in animal deaths occurred near the city baseball stadium within 2 days following the baseball game held in the previous week. He confirms this information, tries to obtain relevant laboratory samples, and confers with the state epidemiologist, who now recognizes epidemiological clue no. 7, dead animals.

Day 3 [*4:00 pm*]

Response: The state health laboratory tentatively identifies *F. tularensis* in a blood sample from a dead animal brought in the previous week, using a new fluorescence assay [101]. Health authorities know that serology for individuals with tularemia is likely to be negative in the first week of illness, and that confirming the diagnosis by serology usually relies on paired sera. The state health agency requests that all blood specimens from those cases associated with the outbreak be tested, and then re-tested once a week for the following month for tularemia using both the fluorescence assay and also for antibody titre. An urgent notification is sent to all local hospital microbiology laboratories that any bacterial culture isolates must be handled with extreme caution due to the risk of spread to laboratory personnel. Epidemiological clue no. 3 (uncommon disease) is confirmed. The case presentation of the grandmother confirms epidemiological clue no. 9, unusual disease manifestation (pneumonic tularemia). The CDC is immediately notified, as is the FBI, and the state's highest elected official (governor's office). Electronic database reporting at the state health agency confirms the additional cases that presented at hospital EDs throughout the area. The state epidemiologist now suspects epidemiological clue no. 1, a highly unusual event with large numbers of casualties. Releases are sent to all local care facilities with an appropriate case definition for reporting suspected cases.

Day 3 [*10:00 pm*]

Response: All state health agency epidemiologists have been requested to work throughout the evening. Additional data is obtained from local health agencies, hospitals, clinical laboratories, medical examiners, veterinarians, and other sources, throughout the evening and into the next day. A network is established by which family practice physicians can be contacted. Additional cases will be identified on day 4, including the 71-year-old male described above.

Day 4 (*Tuesday*) [*9:00 am*]

Scenario: Hospital Emergency Medical Services (EMS) personnel transport a 48-year-old male into Metropolitan City hospital B ED from his home. He has a severe respiratory illness and pneumonia, malaise and myalgia. The patient dies in the hospital from respiratory collapse. Clinical samples from the deceased test positive for *F. tularensis* antibodies.

Response: The state health agency has alerted the media about the outbreak, and has issued a press release to provide information, reassure the public, in addition to notifying the public of the common clinical manifestations in order to bring in and identify unreported cases. The state health agency serves as a *de facto* incident command centre, and reports to the activated state EOC. Communication is ongoing between the state and federal health authorities to determine the need for additional epidemiological assistance and whether additional antibiotic supplies are required through deployment of the SNS. Local physicians' offices and EDs begin to see waves of the worried well.

Information gathered by patient interviews and next-of-kin conducted by the state health agency indicates that the cases had in common attendance at the previous week's baseball game. The state epidemiologist now suspects epidemiological clue no. 4, a point-source outbreak. This assumption is borne out 2 days later when an outbreak curve is derived from the identified cases that indicates a common incubation period, and time period of illness, and a fall in the number of new cases.

Day 4 [*5:00 pm*]

Response: Twenty-three tularemia cases have been identified as part of the outbreak (7 confirmed and 16 suspected). A team of 12 Epidemic Intelligence Service (EIS) officers is sent by the CDC to the state, to assist in the public health outbreak control efforts [102]. The epidemiological link from the cases to attendance at the baseball game is eventually discovered. Environmental samples collected at the ballpark later test positive for *F. tularensis*.

Day 8 (*the second Saturday in July*) [*12:00 pm*]

A communication from an extremist group has claimed responsibility for the outbreak. No additional cases have been reported for the past 24 h. A retrospective Grunow–Finke analysis of the outbreak is conducted, with the result (shown in the Model scenario for deliberate epidemic column in the Table). At this point in the epidemiological investigation, the analysis suggests that a biological attack had occurred (score of 37).

CONCLUSION

In conclusion, the science of epidemiology is a superior foundation for response to a deliberate epidemic (bioterrorism). Identification and management of such an event directly depends upon public health authorities and their capacity for disease surveillance, laboratory, and outbreak investigation. It is important to study the lessons from historical outbreak investigations so as to be able to better determine the difference between deliberate and natural outbreaks. Innovative epidemic assessment tools, such as that developed by Grunow & Finke [29], are useful to help make such differentiation. Maintaining an enhanced index of suspicion, awareness of potential sentinel events, keeping communication open with local health-care providers and law enforcement authorities, and sustaining robust surveillance systems, will together contribute to improving the response to future deliberate outbreaks.

DECLARATION OF INTEREST

None.

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